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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/357,709	07/20/1999	NEIL H. BANDER	242/026	9637

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ART UNIT	PAPER NUMBER
1642	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/357,709	Applicant(s) BANDER, NEIL H.	
	Examiner Jennifer E Hunt	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9-18-2001 ans 1-24-2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-79 and 82-107* is/are rejected.

7)☐ Claim(s) *80 and 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13,17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2001 has been entered.

2. Acknowledgement is made of applicant's cancellation of claims 24, 26-37, and 39-42, and addition of new claims 68-107. Claims 68-107 are pending in the application and considered herein.

Claim Objections

3. Claims are objected to because of the following informalities:

Claim 92 depends from claim 241, and there is not a claim 241. The examiner has interpreted the claim to depend from claim 90.

Claims 92-95 recite the "wherein the antibody or antigen binding portion thereof which comprises..." It appears that "which" should be deleted from these claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 82-95, and 96-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific deposited PSMA antibodies E99, J415, J533, and J591, does not reasonably provide enablement for any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies having variant or altered sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn a method of detecting normal, benign, or cancerous prostate cells in a patient comprising providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, wherein the antibody or binding portion thereof is bound to a

label effective to permit detection of normal, benign, or cancerous prostate tissue, administering the antibody or antigen binding portion thereof to the patient, and detecting the presence of the normal, benign, or cancerous prostate cells by detecting the label which indicates where the prostate cells are localized within the patient. The antibodies claimed encompass any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies which minimally contain incomplete portions of the disclosed antibodies, such as a single CDR which is shared, or antibodies having variant or altered sequences.

The specification discloses the specific deposited monoclonal antibodies E99, J415, J533, and J591. The specification fails to disclose specific guidance or working examples with regard to epitope mapping, or variations of the specific sequences of the disclosed antibodies, including CDR grafting and engineering of the claimed antibodies.

Epitope mapping and alterations of antibody structure are known to be complex and unpredictable. With regard to claims drawn to antibodies which bind to the epitope bound by antibodies E99, J415, J533, and J591, it would require undue experimentation to select and screen for these antibodies. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spatial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include

residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). The specification teaches a competitive binding assay of the antibodies E99, J415, J533, and J591, however, the results do not demonstrate what epitope is bound by the antibodies, or if another antibody could be produced which binds to the same epitope. As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Further, with regard to claims which recite antibodies which minimally contain "binding portions" of various antibody regions (claims 84-95), It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in

maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of the E99, J415, J533, and J591 antibodies, in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide

satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

Therefore, in light of the complexity of the art of epitope mapping and sequence variations and CDR alteration, the lack of guidance and working examples in the specification which would support such variants, and the breadth of the claims, one of skill in the art would not be enabled to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

7. Claims 68-69, 77-79, 96, 98-100, and 107 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al., US Patent 6,150,508, filed November 21, 2000 (IDSAII.)

It is noted that Murphy et al. US Patent 6,150,508 is a continuation in part of application No. 08/827,017, filed March 25, 1997, which is a continuation in part of

application No. 08/621,399, filed March 25, 1996. In order to qualify as prior art under 35 U.S.C. 102(e) over the instant claims, the disclosure of Murphy et al., US Patent 6,150,508 must have support to application 08/621,399, and thus the examiner has only cited the portions of Murphy et al., US Patent 6,150,508 which are supported by application 08/621,399.

Murphy et al., US Patent 6,150,508 teaches a method of detecting normal, benign, or cancerous prostate cells in a patient comprising providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, wherein the antibody or binding portion thereof is bound to a label effective to permit detection of normal, benign, or cancerous prostate tissue, administering the antibody or antigen binding portion thereof to the patient, and detecting the presence of the normal, benign, or cancerous prostate cells by detecting the label which indicates where the prostate cells are localized within the patient (see column 6, lines 50-65, column 11, line 40-column 12, line 26, and column 14, lines 5-40.) Although Murphy et al., US Patent 6,150,508 does not explicitly recite that the patient is a human, this is implicit in the disclosure, which discuses assays of human fluids, humanized antibodies, and tests the antibodies on a human prostate epithelial cancer cell line (LNCAP), and thus the antibodies would function in humans, and would bind to prostate epithelial cells.

Murphy et al., US Patent 6,150,508 further teaches that the antibody can be included with a pharmaceutically acceptable carrier, excipient, or stabilizer (column 50, line 40,) that the antibody can be an antibody which binds live cells and /or is an

IgG (column 9, line 50-column 10, line 16, column 7, lines 1-5,) that the antibody is a monoclonal antibody (column 6, lines 50-65,) that the antibody can be a Fab fragment, a $F(ab')_2$ fragment or an Fv fragment (column 10, line 35-55, column 11, lines 30-40, and column 14, lines 5-30.) Murphy et al., US Patent 6,150,508 further teaches that the label can be a fluorescent label or a radiolabel (column 14, lines 5-30.)

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 68-79 and 96-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al., US Patent 6,150,508, patented November 21, 2000, in view of Thomas et al., Antibodies, A practical approach, Vol. 2, 1988, or Schlom et al. Molecular Foundations of Oncology, chapter 6, pages 95-134 (IDS AZ.)

Murphy teaches as applied to claims 68-69, 77-79, 96, 98-100, and 107. Murphy fails to teach the specific imagining techniques and antibody characteristics which are recited in the dependent claims, specifically, that the label is detected using an imaging device, that the administration of the antibody is carried out parenterally, intravenously, by intracavity instillation, or rectally, wherein the label is detected

using a transrectal probe, wherein the antigen is administered following a prostatectomy, that the antibody is internalized with the prostate specific membrane antigen, that the label is a short range radiation emitter, and that the label is selected from the group consisting of (^{212}Bi, ^{213}Bi, and ^{211}Ar), or (^{32}P, ^{125}I, ^{3}H, ^{14}C and ^{188}Rh), or ^{131}I or ^{99}mTc, or ^{111}I.

These specific imagining techniques and antibody characteristics are well known in the art, as set forth in applicant's disclosure of admitted prior art at pages 19-22, or as set forth for example in Thomas et al., Antibodies, a practical approach, Vol. 2, 1988 teaches that antibodies can be used for in vivo imaging, including an imaging device, antibody internalization, and radiation emitters including ^{131}I or ^{99}mTc, or ^{111}I. Also, Schlom et al. teaches that antibodies can be used for in vivo imaging, including an imaging device, intravenous and intracavity administration, antibody internalization, and radiation emitters including short range radiation emitters, ^{125}I, ^{131}I or ^{99}mTc, or ^{111}I. Further, monitoring patients as set forth in Murphy et al., US Patent 6,150,508 would encompass monitoring patients after a prostatectomy, which is the art standard treatment for early stage prostate cancer.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the assays taught in Murphy et al., US Patent 6,150,508, and one would have been motivated to do so because these techniques are art recognized equivalents and variations for diagnosis and therapy.

Allowable Subject Matter

Claims 80 and 81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 80 and 81 are objected to. Claims 69-79 and 82-107 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

SHEELA HUFF
PRIMARY EXAMINER

jeh
April 8, 2002